Comparative Effectiveness Research

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Comparative Effectiveness and FDA

FDA's experience with comparative effectiveness claims is relatively limited. Our enabling law (FDC Act, as amended in 1962) does not require assessment of comparative effectiveness and the legislative history made it very clear there was no relative effectiveness requirement. A new drug does not have to be better than, or even as good as, existing treatment.

An important exception is in situations where there is an existing effective treatment for a serious illness that cannot be denied patients. In that case sponsors conduct non-inferiority studies that seek to rule out a treatment difference between the new drug and the active control of unacceptable size. But these trials

1. Do not usually show superiority.
2. Do not really show "equivalence." Rather they show that a reasonable fraction of the effect of the control is preserved.

Comparative Effectiveness

We see relatively few serious attempts at assessments of comparative effectiveness. A fair number of trials do have active controls as well as placebos, common in studies of pain, depression, and hypertension, but the active control is there to establish assay sensitivity, i.e., to show that the study is capable of detecting the effect of the active drug vs placebo, and the trials are rarely sized for a valid comparison of the active drugs.

[They could be sized that way; they just aren't. The active drug groups would need to be very large to show a small difference, e.g., a difference of 25% of the drug-placebo difference.]

Superiority Claims

There are several possible kinds of superiority that could be shown.

1. Overall superiority in effectiveness in the general population.

2. A safety advantage in the general population.

3. Advantages in subsets
   - Greater effectiveness in non-responders to another drug
   - Better tolerability in people with an adverse effect on another drug
   - Effectiveness in a genomically or proteomically defined subset
   - Other: better compliance (o.d. dosing) leading to better outcome

Overall Superiority

Not commonly shown or even attempted, but superiority claims have been sought at times and our standard for assessment has been the approval standard: adequate and well-controlled studies (usually more than 1). Moreover, the studies must be fair, as discussed in ICH E-10 [Choice of Control Group and Related Issues in Clinical Trials, 2001]. A comparison could be unfair if:

- Low dose of the comparator was used.
- The patient population had previously failed the older drug (but see below; a good study can be run in this population).
- Selection and timing of endpoints favored one drug.

Superiority Claims (cont)

It is not easy to get such a claim, but there have been successes in oncology and elsewhere.

- Two large studies showed candesartan had a larger blood pressure effect than losartan (in labeling).
- LIFE study (losartan vs atenolol) showed superiority vs stroke, but in only one trial. Losartan got stroke claim, but not a direct comparative claim.
- Prasugrel was more effective than clopidogrel in decreasingly the rate of heart attacks in people with acute coronary syndrome (it caused more bleeding too).
- PPIs have claims vs H2 blockers.
- Anastrazole is superior to tamoxifen as adjuvant Rx post surgical treatment of breast Ca, especially in ER positive.
- Irbesartan delayed decline in renal function in type 2 diabetes; it was superior to amlodipine, which had no effect.

Superiority Claims (cont)

We thus use the legal effectiveness standard for what is, in fact, a claimed effect, just as the law demands. It is a high standard, but it is not easy to see how a lesser standard would fit the law nor (my opinion here) whose interest such a standard would serve.

And we can be certain that people, will if given the opportunity use lower quality data to make such claims. We know that before there was an effectiveness standard, the effectiveness of thousands of drugs and more thousands of claims were unsupported and proved unsupportable. We know that claims for dietary supplements, unencumbered by any requirement for controlled studies, are rarely unsupported by such trials. It is not easy for me to see a public interest in the proliferation of comparative effectiveness claims based on data known to be unsuited to the purpose.

Superiority in a Subset (Non-responders)

A very attractive study design, so much a set-up it seems almost unfair, is to study a drug in failures on another therapy or in people who cannot tolerate other therapy. Strictly, this is not comparative effectiveness, but it is very useful to know. Oddly, this is rarely attempted properly, which requires randomizing patients back to the failed or poor tolerated treatment as well as the new drug.

I'm aware of only 4 attempts to show an effect in non-responders, 3 successful – clozapine, bepridil, and captopril, and these drugs were approved only because they had these data, and one total failure, rofecoxib in celecoxib non-responders.

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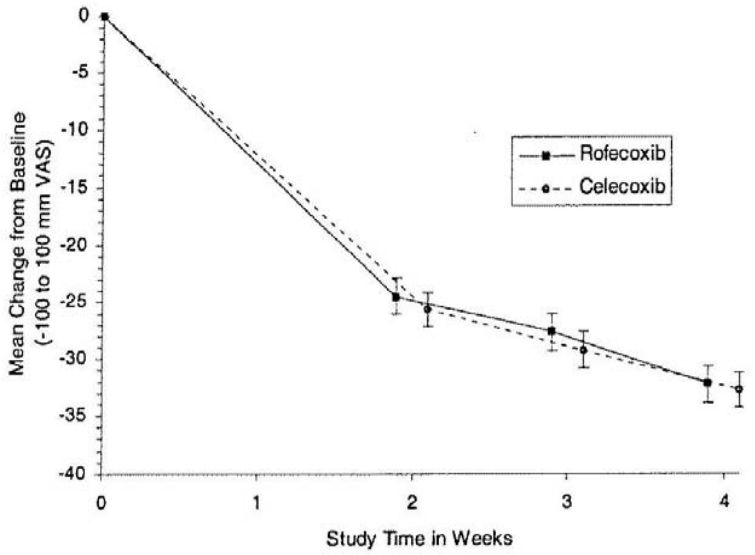
Figure 1

Pain at Night while in Bed (WOMAC)
Mean Change from Baseline ± SE by Timepoint
(Primary Per-Protocol Approach)



Note that without a celecoxib control, rofecoxib would have appeared VERY effective in this NR population.

Superiority in a Subset (cont)

There have also been few attempts to show better tolerability in people who had adverse effects on another drug, again by randomizing patients back to the poorly tolerated drug and the new drug.

- It was clearly shown that losartan did not induce cough in patients who reliably coughed on lisinopril.
- Wellbutrin was shown not to affect female sexual function in patients whose function was impaired with SSRI's.

If there are more of these I'm not aware of them.

Superiority in a Subset (cont)

It would be easy to use genetic information to identify patients who would do better on one day than another. An easy case would be to study people who do not form the active metabolite of a drug because they lack a CYP450 enzyme of such drugs as tamoxifen or clopidogrel.

Not really superiority but a very informative study is one that adds a new treatment to established therapy (add on study), showing an additive effect. This has been done for a wide variety of treatments: for heart failure, hypertension, CAD, pain, etc.

Comparative Effectiveness

The excitement is palpable. . . And why not?

Despite the paneity of comparative trials, the are very important. Clinically, after knowing a drug works and is safe (which FDA takes care of) most of the important questions about drugs are comparative, i.e., deciding which drug to choose

- Does it work better than alternatives? Faster?
  - In all patients
  - In a subset
- Can you add it to other treatments?
- Does it have some additional benefit in some or all patients?
- Does it work when others fail?
- Is it about as good, but cheaper?

But there usually isn't much of such data

- Drug companies historically have not done proper comparisons (with the critical exception for situations where active control trials are ethically necessary)
- Trials almost never have > 1 comparator; usually interest is in comparing all members of a class
- Trials rarely compare across classes
- Trials usually are too small to give definitive answers

Comparative Effectiveness

So the medical need for comparative data is great and apparent.

We also need to acknowledge a major interest in costs of therapy. All of us, payers too, will pay for a more expensive treatment with an advantage

- maybe after other therapy fails
- maybe it depends on how much advantage

but there is great reluctance to pay more for the same effect. So a major interest of payers is showing whether there is an advantage. (Could they just agree to pay only when one is shown?)

But wanting comparative data does not necessarily mean we know how to get comparative data of high quality with reasonable effort and at acceptable cost.

And it must be of high quality. Mistakes will greatly undermine the credibility of the effort, not to mention the harm they could do.

Comparative Effectiveness Is Not the Only Need

I realize there is current enthusiasm for comparative effectiveness, but we need to keep our balance. If there is to be funding for trials there are other critical issues too. For example:

1. Do our physical therapy and non-pharmacologic psychiatric interventions work at all? Many are untested.
2. How can we improve compliance/persistence with vital chronic therapy (lipid-lowering, BP, diabetes control, smoking cessation, weight reduction)? Could cluster-randomized trials help?
3. How low should we push LDL, BP, BS; is it the same for everyone? How many anti-platelet treatments should we give in ACS and after PCI and how long should we give them?

The right determination of what to study is the value of what we'd learn, not whether it is comparative. The best study may be a comparison of a treatment with no added treatment. The IOM list of 100 is very consistent with this.

Comparative Effectiveness Issues

Comparative effectiveness raises a host of issues, all of them interesting and most of them matters of long FDA and personal interest, including

1. How we obtain evidence of comparative effectiveness and safety: role of trials, meta-analyses, observational data.

2. Often (? usually) you're interested in comparisons with multiple drugs, not just one, frequently drugs in different pharmacologic classes. How to compare multiple treatments is challenging and doing it is costly.

Comparative Effectiveness Issues

3. There are major challenges in doing comparative effectiveness trials

- Differences between effective treatments will, at most, be small, so that
  - Trials will need to be very large to show them
  - Nothing but an RCT will be credible

- Showing there is no (or not much) difference between treatments, often the goal of the comparison, is also very hard, will often need a placebo group to assure assay sensitivity, and again, trials may need to be very large, depending on the size difference to be ruled out

- Efficiency and simplification are critical

Comparative Effectiveness

You Need Randomized Trials (Maybe Meta-analyses)

With rare exceptions, differences between drugs, if any, will be small, considerably smaller than the whole effect of the drugs, which themselves are often small. And the difference you want to rule out is also small.

A blockbuster outcome study in CHF, hypertension, CAD will reduce event rates by 40%. Far more commonly, it will be more like 20%. If the whole effect of the drug, i.e., an HR of 0.8, a complete loss of that effect (1 ÷ 0.8) would give an HR of just 1.25 for the comparison of a new drug vs the standard; i.e., it would be only 25% worse.

But between-treatment differences of interest, or the difference to be ruled out, will not be the whole drug effect, but smaller: suppose you would want to detect a loss of half of the 20%, a 10% difference. In that case the HR for the inferior drug, the upper bound of the CI for new/old, would be just 1.125, i.e., very hard difference to detect.

In terms of risk, that means you're trying to detect a risk ratio of 1.1-1.2 at most. This is possible in large ambitious RCTs, but you cannot reliably detect such differences in anything but randomized trials.

Comparative Effectiveness

You Need Randomized Trials (cont)

Symptomatic conditions pose at least as great a problem, at least usually (and one might ask how important it is to rule out or document small differences).

Trials of antidepressants fail about 50% of the time (cannot distinguish drug from placebo) and a typical effect size is 3 HamD points (drug-placebo). Trials these days are 100-200/arm.

A large between-drug difference could conceivably be 1.5 HamD points (that would be a very large difference and, usually, the less effective agent would have had difficulty beating placebo). Far more likely would be a difference of 1.0 HamD point or less.

Trials to show such differences would be enormous. Moreover, failing to show a difference would be meaningless without a placebo group to assure assay sensitivity (ability of the study to detect effects).

Most symptomatic conditions are like this, except where effects are huge (Tysabri vs interferon, a difference so large it is obvious in cross-study comparisons).

Comparative Effectiveness
You Need Randomized Trials (cont)

It is not insulting to observational/epidemiologic approaches to say that they are generally unreliable when trying to detect risk ratios of < 1.5, and certainly when looking for risk ratios of 1.2 and less. It is not a lack of power. What makes such approaches tempting is in fact their huge power and speed.

But those advantages do not make up for potential bias and confounding. There are many sobering examples. Let me give two:

Hormone replacement therapy
Calcium channel blocker toxicity

The incorrect results of epidemiologic studies in these cases, unfortunate at best, disastrous at worst, did not usually arise from obvious methodological flaws or foolishness. The methods are just not reliable for small differences, usually because without randomization you cannot assure the needed close similarity of the groups receiving each treatment.

Hormone Replacement Therapy

Although observational studies did not give uniform results, hormone replacement therapy was thought to reduce coronary heart disease (CHD) by 40-50%. The Women's Health Initiative randomized > 16,500 post-menopausal women 50-79 to HRT (0.625 oral equine conjugated estrogens + 2.5 mg medroxyprogesterone acetate) or placebo.

Despite favorable effects on LDL and HDL cholesterol and triglycerides, coronary heart disease effects were adverse

	HRT 8506	Placebo 8102	HR	95% CI
CHD	188	147	1.24	1.00-1.54
NFMI	151	114	1.28	1.00-1.63
Fatal CHD	39	34	1.10	0.70-1.75
CHD, revasc, angina	369	356	1.00	0.86-1.15

HRT

HRT has obvious short-term benefits but the case for CHD prophylaxis, although plausible (women have less CHD than men while producing hormones and catch up with men after menopause) and epi-supported, was not only not made, but CHD harm was strongly suggested.

There were also increases in breast Ca, thrombophlebitis, pulmonary emboli.

Calcium Channel Blockers

The full CCB story deserves a book, not a few slides. Over the course of several years, roughly 1995 through 2002, cohort and case control studies, almost all of them comparing CCB's with other antihypertensive drugs, suggested that CCB's:

1. Increased the rate of AMI (Psaty, et al, JAMA, 1995).

2. Increased mortality (Furburg and Psaty, Circulation, 1995); this was actually a subset of a meta-analysis of nifedepine).

3. Increased mortality (Pahor, et al. J Am Geriatrics Society, 1995, a cohort study). Oddly, verapamil was protective; diltiazem, nifedipine AND ACEIs all gave RR's of 1.5-1.9.

Calcium Channel Blocker (cont)

4. Increased GI bleeding (Pahor, Furburg, et al Lancet 1996; Kaplan, Furburg, Psaty, Letter to Age and Aging, 2002).

5. Increased risk of all cancer (Pahor, et al Lancet, 1996). Oddly, risk was up for verapamil and nifedipine, not at all for diltiazem.

6. Increased breast cancer (Fitzpatrick, Furburg, et al, Cancer, 1997).

7. Caused suicide (Melander, BMJ, 1998).

Calcium Channel Blockers

FDA's Cardio-Renal AC saw the mortality and AMI data (probably in 1995-6) and did not find it persuasive. HRs were mostly in the 1.5-2 range and varied considerably from drug to drug.

To my best knowledge, none of these findings were confirmed in RCTs (ALLHAT, various CAD trials of verapamil and diltiazem). The findings were discussed, condemned, supported in dozens of papers. A Sounding Board piece (NEJM) in 1997 by Deyo, Psaty, and others described manufacturers' attempts to gain access to Psaty's records related to the 1995 AMI study, as well as many hostile academic (perhaps manufacturer-supported) critiques, citing this as a classic case of attacking scientific results that run counter to financial interests and strongly-held beliefs. That surely could be part of it but there were certainly scientifically sound bases for criticism as well. Paper (can't find) comparing industry support for authors supportive and opposed to the CCB findings. Guess which ones had more support.

Calcium Channel Blockers

People can form their own views as to what all this illustrates. Among other things it shows

1. Inadequate attention to description and presentation of epi results. Epi studies need careful protocols that record changes, well-described hypotheses, correction for multiple hypotheses (i.e., all the things we've learned to ask about RCTs).

2. Particular risks when the adverse effect is a possible consequence of the disease, where the severity of the condition and the effect of treatments can be confounded.

3. RR's < 2 need great care and should be viewed very skeptically (although they can surely generate hypotheses). Comparative effectiveness will almost invariably be about RR's < 1.5 and indeed < 1.2, a major challenge.

4. Epi errors can cause major disruptions and conflicting data are inevitable.

Calcium Channel Blockers

With recognition of the need to get BP under better control, CCB's must be used in many people. They may even have advantages in some populations. But their use was somewhat marginalized for many years because of these concerns. There is little of that concern expressed in JNC VII (2004), so perhaps the damage has passed.

WE DO NOT WANT ERRORS. The questions addressed in comparative studies, especially outcome studies, matter. To get correct answers, the comparisons need RCTs unless differences are very large. They hardly ever are.

Comparative Effectiveness - Difficulties

1. Multiple Drugs of Interest

What physicians really want to know is how all (or at least many) members of a class compare. This is not easy, for many reasons.

1. For many comparisons you need a placebo to assure assay sensitivity, a potential problem for post-approval, often large, studies.

You can sometimes use a NI study design where there is a solid basis for knowing the effect of the positive control in an NI study, but that would be impossible in depression, anxiety, and most symptomatic conditions; for those you need a placebo to show ASSAY SENSITIVITY, i.e., that you can tell one thing from another, because many studies in those conditions cannot tell active drugs from placebo [You could show superiority without the placebo, but not similarity].

Comparative Effectiveness – Difficulties

2. Hard to expect a company to study multiple drugs in one study.

Separate comparisons don't really tell you what is needed; you can't usually compare across studies.

Multiple comparisons have been carried out by government: ALLHAT and CATIE

- ALLHAT – chlorthalidone, lisinopril, doxazosin, and amlodipine

Ambitious but results hotly debated; there were design problems (couldn't add diuretic to lisinopril). Meta-analyses and another large trial suggested different answers.

ALLHAT clearly did show that cheapest drug (chlorthalidone) was a reasonable start, but drugs have different properties: some treat diabetic nephropathy (ARBs), CHF (ACEI's, BBs, diurectics), angina (CCBs, BBs), or post-infarction (BBs, maybe ACEI's).

ALLHAT

Wonderful Intent, Hard Trial

Compared – clorthalidone, lisonopril, amlodipine, and doxazosin.

Some element of interest in cost: "Are newer types of anti-HT, which are currently more costly. . . as good as or better than diuretics in reducing CHD incidence and progression" (abstract, Am J HT, 1996; 9: 342-360).

Problems:

1. Plainly, ALLHAT was an NI study, but no discussion if NI margin for any endpoint. Doing so would have been difficult because regimens did not match past effective regiments and population (enriched for black patients) was not the same. Did this disadvantage lisinopril? The question is, then, what does failure to see a difference mean? It is very hard to know and, to my best knowledge, was not addressed.

ALLHAT

Problems (cont)

2. No beta-blocker group.

3. Treatments did not get usual accompaniments because you could not add another test drug.

   E.g., could not add diuretic to lisinopril. This is particularly critical for black population and for CHF (all CHF studies of ACEI's were added to diuretic). Lisinopril thus had slightly poorer control of BP.

4. ACE inhibitors were superior for CV events in a different study, the Second Australian National Blood Pressure Study (HCTZ, mostly white).

5. Did we learn enough? I'd say yes: main lesson is that it doesn't matter too much how you get the BP down.

Comparative Effectiveness – Difficulties

- CATIE

  NIMH: 4 atypical (olanzapine, risperidone, quetiapine, ziprasidone), one typical (perphenazine) anti-psychotics used in schizophrenia showed olanzapine was most effective (fewest D/C for lack of effectiveness) and least well-tolerated (most D/C for intolerance). CATIE worked because there were differences. Had there been no differences, it would have, absent placebo, been uninformative.

  Both ALLHAT and CATIE were very expensive. Clearly worth it, in my opinion, but at those prices can't do too many.

CATIE

1493 schizophrenics randomized to olanzapine, perphenazine, quetiapine, or risperidone (later ziprasidone).

Endpoint was "discontinuation" of treatment for any cause.

Outcome	Olanz 330	Quet 329	Risp 333	Perph 257	P-value
All DC (%)	64	82	74	75	< 0.002
Lack of E (%)	15	28	27	25	< 0.001
Intolerability (%)	18	15	10	15	

Comparative Effectiveness – Difficulties

2. Sample size is very large

Suppose you wanted to compare anti-depressants. Current studies vs placebo these days use 100-150 patients per group to show a drug-placebo difference of 3-4 HamD points. You need placebo for assay sensitivity. What HamD difference do you want to rule out?

2 points – no chance it's that large

1 point – sample size for active drug would be many hundreds, perhaps 1000. Is that really feasible?

Comparative Effectiveness - Difficulties

Given the problems (multiple drugs of interest, small effect sizes) it is tempting to seek alternative data sources, notably meta-analyses and cross-study comparisons. The problem is that in a cross-study comparison patients are not randomized to treatments and patients on one drug may differ from patients on another, making such comparisons treacherous. The problems and potential biases in meta-analyses are well-recognized, but at least potentially, these are well-randomized comparisons.

Possibilities

The problems I've described can perhaps be overcome, if there is enough interest. Possibilities include

- Doing large studies in treatment environments already collecting data (HMO's, VA), perhaps using internet to enroll, gain consent, follow PRO outcomes. These would not select too much, i.e., we're talking about very pragmatic trials. We know very large trials in Europe (ISIS, GISSI) had reasonable costs.

  If patients and doctors were "into" this, maybe it wouldn't cost too much.

- Placebos are, at least now, hard to use in the real world but you don't need one to show superiority. But in symptomatic conditions, absence of a placebo will lead to inability to interpret results if no treatment is superior.